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ABSTRACT

The effect of pentobarbital anesthesia upon the minimal voltage and current required for electrical ventricular defibrillation (the defibrillation threshold) was investigated in dogs. Threshold current, energy, and charge in five dogs averaged 2 per cent, 13 per cent, and 6 per cent less under surgical levels of pentobarbital anesthesia than thresholds in the same animals in the awake, unanesthetized state. In dogs given sufficient pentobarbital to produce apnea and supported by mechanical ventilation, threshold current, energy, and charge averaged 3 per cent, 17 per cent, and 2 per cent less than comparable awake values. These differences were far from statistically significant. In a second study, five dogs were kept for 8 to 10 hours at a surgical level of anesthesia with pentobarbital sodium. Defibrillation threshold current, determined at hourly intervals, did not drift outside ± 10 per cent limits. Arterial blood gas measurements revealed a stable, compensated metabolic acidosis in all animals (pH 7.36 ± 0.06, pCO_2 33 ± 4 mm. Hg, pO_2 71 ± 9 mm. Hg). These data support the validity of defibrillation studies using animals anesthetized with pentobarbital and indicate the stability of the defibrillation threshold under controlled experimental conditions.

Key words: animal model, cardiac arrest, confounding variable, stability, validity, ventricular fibrillation

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INTRODUCTION

Electric shock applied across the chest or directly to the heart is the only practicable means for termination of ventricular fibrillation, an otherwise lethal cardiac arrhythmia. [1] The shock strength required for defibrillation of the ventricles depends upon body weight in animals and in man, [2-5] but also may be influenced by physiologic factors such as myocardial ischemia, electrolyte imbalance, drug action, and body temperature. [6-8] Knowledge of the factors which determine the shock strength necessary for defibrillation is important because a shock which is too weak may fail to defibrillate, and a shock which is too strong may damage the heart. [9-10] All controlled experimental studies of electrical ventricular defibrillation reported to date have used anesthetized animals as subjects--in most cases barbiturate anesthetized dogs. In contrast, virtually all clinical ventricular defibrillations outside the operating room are carried out in unanesthetized patients in settings such as the coronary care unit or emergency room. Recently the barbiturate anesthetized dog has been criticized as a model of normal cardiovascular physiology. [11] Since no study can be found in the literature reporting the influence of anesthesia on the efficacy of electrical defibrillation, a reasonable question may be raised about the validity of anesthetized animal models used for defibrillation studies.

The author has reviewed 58 reports, dated 1899 to 1975, concerning the efficacy of electric shock for the termination of cardiac fibrillation in animals. In only one study was no anesthesia employed routinely. In 37 of 58 studies injectable pentobarbital sodium was the only anesthetic used in a particular species. In 10 of the studies thiopental sodium was employed, either alone or in combination with inhalation anesthetics and muscle relaxants. In six of the studies a mixture of halothane, nitrous oxide, and oxygen was used, often after the induction of anesthesia with intravenous thiopental sodium. The use of a variety of other anesthetic agents for defibrillation studies has been reported, including sodium barbital, glycerol guaiacolate, morphine, and chloralose. In 52 of the 58 studies dogs were used as experimental subjects. In particular the pentobarbital anesthetized dog was used in 36 (62 per cent) of the defibrillation studies.

Unquestionably, anesthetic agents of all kinds have direct effects upon excitable biologic membranes. Although the central nervous system is the most important site of action of general anesthetic agents, many anesthetics, including pentobarbital, are known to affect the mechanical and electrical performance of cardiac muscle. The amplitude and strength of myocardial contraction are depressed by cyclopropane, diethyl ether, nitrous oxide, and halothane, as well as by barbiturates including pentobarbital, secobarbital, and thiopental. [12-16] Hydrocarbon anesthetics may depress the rate of activity of the sinus node pacemaker as well as the speed of AV and intraventricular conduction. [13, 17] Significant differences in the response of the dog heart to the AV blocking and arrhythmogenic actions of digitalis glycosides have been reported for animals anesthetized with pentobarbital vs. halothane, vs. methoxyflurane. [18] Cyclopropane, halothane, and to a lesser extent thiopental are known to sensitize the myocardium to the arrhythmogenic effects of epinephrine. [19] Accordingly, it is quite conceivable that anesthetics could alter those parameters of cardiac electrophysiology which determine the success or failure of electrical defibrillation.

It is generally accepted that during the induction of anesthesia the relative lipid solubility of general anesthetics and the generous blood flow to the brain cause initial concentration of these drugs in the central nervous system. After maintenance of anesthesia for several minutes to several hours, however, these drugs become widely redistributed in peripheral tissues, including the myocardium. [20-22] If there were a significant effect of anesthetics upon the determinants of electrical defibrillation, one might reasonably expect a gradual drift of the threshold voltage and current for defibrillation over the course of experiments using anesthetized animals as subjects. Control studies demonstrating the presence or absence of such a drift in defibrillation threshold over time intervals greater than one hour have not been reported to date. Accordingly, the following studies were undertaken to determine (1) if the induction of anesthesia with intravenous pentobarbital sodium in the dog alters transchest defibrillation threshold, and (2) if the maintenance of a stable surgical level of anesthesia with pentobarbital sodium for 8 to 10 hours is associated with a change in the defibrillation threshold.

METHODS

Study 1. Effect of pentobarbital anesthesia.

Five dogs of mixed breed, weighing 6 to 14 kilo grams, served as subjects. Initially each dog was anesthetized with injectable pentobarbital sodium (Nembutal, 50 mg./ml. in a 10 per cent alcohol, 40 per cent propylene glycol vehicle, 25 to 30 mg./Kg. intravenously). No preanesthetic medication was given. A bipolar catheter electrode was placed in the right ventricle of the heart via a right jugular venous cut-down, using sterile technique. Position of the catheter electrode within the heart was verified by recording the catheter tip electrogram and comparing its timing with the electrocardiogram (ECG) Lead II. The catheter was stabilized in the jugular vein and the wound was closed with 2-0 silk sutures. The external portion of the catheter was protected with an adhesive elastic bandage placed around the neck and a soft collar 8 cm. in width.

After a recovery period of 36 to 72 hours the defibrillation threshold was determined before and after induction of anesthesia with pentobarbital. These investigations in unanesthetized and anesthetized subjects were carried out in accordance with National Institutes of Health and institutional guidelines for the use of laboratory animals. [3, 24]. Defibrillation threshold in awake, unrestrained animals was measured as follows: ECG Lead II electrodes were applied to the limbs and the position of the catheter electrode was confirmed by recording the catheter tip electrogram. Defibrillating electrodes, held in position with rubber straps, were applied to the shaved skin of the thorax with electrolytic jelly, one centered over the apex beat area and the other in the opposite position on the right chest wall. The defibrillating electrodes were stainless steel discs, 2 mm. thick and 8 to 10 cm. in diameter (20 per cent of the animal's chest circumference ± 1cm.). The standard location of each electrode was outlined in ink on the thorax.

Ventricular fibrillation was produced by the application of a 1 second train of 60 Hz, 2 msec. duration rectangular electrical pulses of 5 to 15 volts intensity via the right ventricular catheter. Ventricular fibrillation was confirmed by the presence of random waves in the electrocardiogram

and by the descending level of consciousness of the subject. As the animal lost consciousness it was placed in dorsal recumbency.

The defibrillator employed contained a 16 microfarad capacitance, a 44 milihenry inductance, and a 7 ohm internal resistance in series with the subject. A 1.00 ohm, 100 watt resistor in series with one electrode was used for measuring current output. The peak output voltage of the defibrillator could be varied continuously from 0 to 7,000 volts. The duration of the delivered current pulse, slightly dependent upon subject resistance, was typically 4 to 5 msec. The wave-form of the current pulse was a heavily damped sinusoid.

As soon as possible after the confirmation of ventricular fibrillation, (15 to 45 seconds after endocardial stimulation), a defibrillator shock, calculated to be adequate for defibrillation on the basis of the dog's body weight as described by Geddes and colleagues [2] was delivered at the time of end-expiration. The voltage and current applied to the subject were measured using a Tektronics model D-11 dual channel storage oscilloscope. Defibrillation was confirmed by return of the femoral pulse and QRS complexes in the electrocardiogram. With return of consciousness the animal was allowed to right itself. After a recovery period of about 2 minutes, the heart was refibrillated and defibrillation was attempted with a voltage setting 5 to 10 per cent less than that of the previous trial. This procedure was repeated until the animal was not defibrillated by the first shock, whereupon a stronger shock was applied immediately to restore cardiac pumping action.

Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles. Only data from the first shock delivered after the onset of fibrillation were used in calculation of threshold. In this study threshold values were considered adequately precise if they differed no more than 10 per cent from values unable to defibrillate the ventricles. Delivered energy and charge were calculated as described by Babbs and Whistler. [25] Twenty minutes after the defibrillation threshold was determined in the unanesthetized animal, intravenous pentobarbital sodium (25 to 30 mg./Kg.), was given to produce surgical anesthesia and the defibrillation threshold measurement was repeated with the animal in dorsal recumbency. After a three day recovery period, another set of threshold determinations was made in the awake and anesthetized states.

On the final day of testing, the defibrillation threshold was determined following larger doses of pentobarbital. After the routine threshold determination under surgical anesthesia, sufficient intravenous pentobarbital was given to produce apnea and the threshold measurement was repeated. Then sufficient intravenous pentobarbital was given to produce circulatory shock (defined as systolic blood pressure less than 50 mm. Hg measured via a catheter placed in the abdominal aorta) and a final threshold determination made within 10 minutes. During apnea and shock the animal was maintained using mechanical ventilation sufficient to produce a respiratory minute volume, measured with a Wright respirometer, roughly equal to that measured under surgical anesthesia.

Study 2. Stability of defibrillation threshold under pentobarbital anesthesia.

Five dogs of mixed breed, 5 to 16 kilograms in weight, conditioned in captivity for a period of at least two weeks, and disease-free by physical examination, were used in this study. Each animal was anesthetized with intravenous pentobarbital sodium (25 to 30 mg./Kg.). No other drug, except normal saline, was administered at any time. The trachea was intubated and the animal placed in dorsal recumbency for the duration of the study. The urinary bladder was catheterized with a No. 8 French filiform catheter connected to a closed volumetric drainage bottle. Mean aortic blood pressure was measured using a mercury manometer, and respiratory minute volume was measured with a Wright respirometer. Arterial blood pH, pCO_2, and pO_2 were monitored using an Instrumentation Laboratories Model 213 blood gas analyzer. Disc electrodes of 8, 10, or 12 cm. in diameter (20 per cent of the chest circumference ± 1 cm.) were applied to the shaved skin of the right and left hemithoraces with electrolytic jelly and sutured in place. One electrode was centered over the apex beat of the heart and the other was located at a corresponding position on the right chest wall, 3 cm. cephalad of the left electrode. Defibrillation threshold was determined once every hour using the method described for Study 1. The values of mean aortic blood pressure, respiratory minute volume, urine output, arterial blood gases, and esophageal temperature were recorded at half-hour intervals. A stable level of surgical anesthesia was maintained in each animal by the intravenous administration of 2 to 5 mg./Kg. maintenance doses of pentobarbital sodium each hour. Saline solution, 0.9 per cent, was given in quantities of 1 to 2 ml./Kg./hr. by vein. Esophageal temperature was maintained in the range of 36 to 39° C. with the aid of warm overhead lights.

RESULTS

Study 1. Effect of pentobarbital anesthesia.

In all five dogs comparisons could be made between defibrillation thresholds in the awake and the anesthetized states. In one dog, three successive comparisons of awake vs. anesthetized threshold values were made during a 12-day period. Threshold current data for this animal are plotted in Fig. 1. The ratios of the threshold peak current for all dogs at all levels of anesthesia to the average threshold under surgical anesthesia for each animal, are plotted in Fig. 2. No consistent effect of pentobarbital anesthesia on the ventricular fibrillation threshold is evident. Mean values of threshold shock strength (on the final day of testing) in terms of peak current, delivered energy, and delivered charge per kilogram of body weight are given in Table I. One-way analyses of variance indicate that the observed effects of anesthesia level upon threshold current, energy, and charge are far from statistically significant, as indicated by the p values in the table.

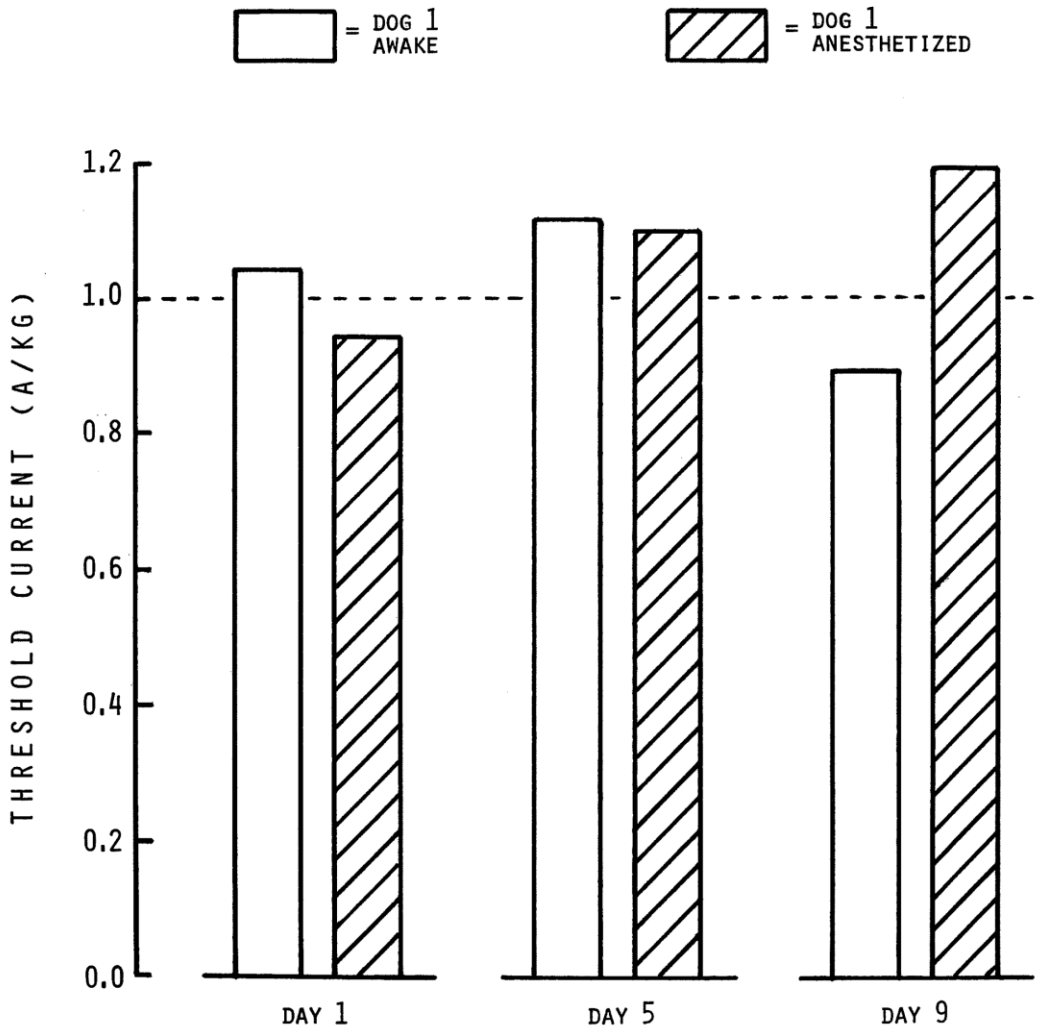

Fig. 1. Threshold peak current for ventricular defibrillation in unanesthetized and anesthetized states on successive trials in the same animal. On three successive trials the threshold current in the unanesthetized animal was greater than, equal to, and less than the threshold current after induction of pentobarbital anesthesia. Mean threshold before anesthesia = 1.02 A/Kg; mean threshold after anesthesia = 1.08 A/Kg. Threshold data for the unanesthetized dog were reproducible within ± 10 per cent limits.

Table I. Mean defibrillation threshold* at 4 levels of anesthesia

	Awake	*Surgical anesthesia*	*Apnea*	*Shock*	*F ratio*	*p value*
Peak current (amps/Kg.)	1.25 ± .28	1.22 ± .17	1.21 ± .18	1.13 ± .21	0.21	0.89
Delivered energy (w-s/Kg.)	1.55 ± .77	1.35 ± .46	1.28 ± .42	1.11 ± .17	0.51	0.68
Delivered charge (m coulombs/Kg.)	2.31 ± .41	2.18 ± .25	2.26 ± .43	2.06 ± .39	0.43	0.73
Number of observations	7	11	4	3		

*± 1 S. D.

The response of unanesthetized dogs to the fibrillation-defibrillation procedure is worthy of mention. Typically, the dogs were not alarmed by the intracardiac electrical stimulation used to induce fibrillation. The loss of cerebral blood Bow due to ventricular fibrillation produced initial excitation, lasting 5 to 15 seconds, which rapidly diminished as the animal lost consciousness. Delivery of defibrillating current caused a brief, forceful contraction of thoracic and abdominal musculature, resulting in vocalization. Animals for whom the total circulatory arrest time was less than 30 seconds rapidly regained consciousness, and assumed a sitting or standing position. Animals for whom the total circulatory arrest time was 30 to 60 seconds did not regain consciousness as soon after defibrillation. These animals remained in dorsal recumbency after resuscitation and appeared dazed or tranquilized.

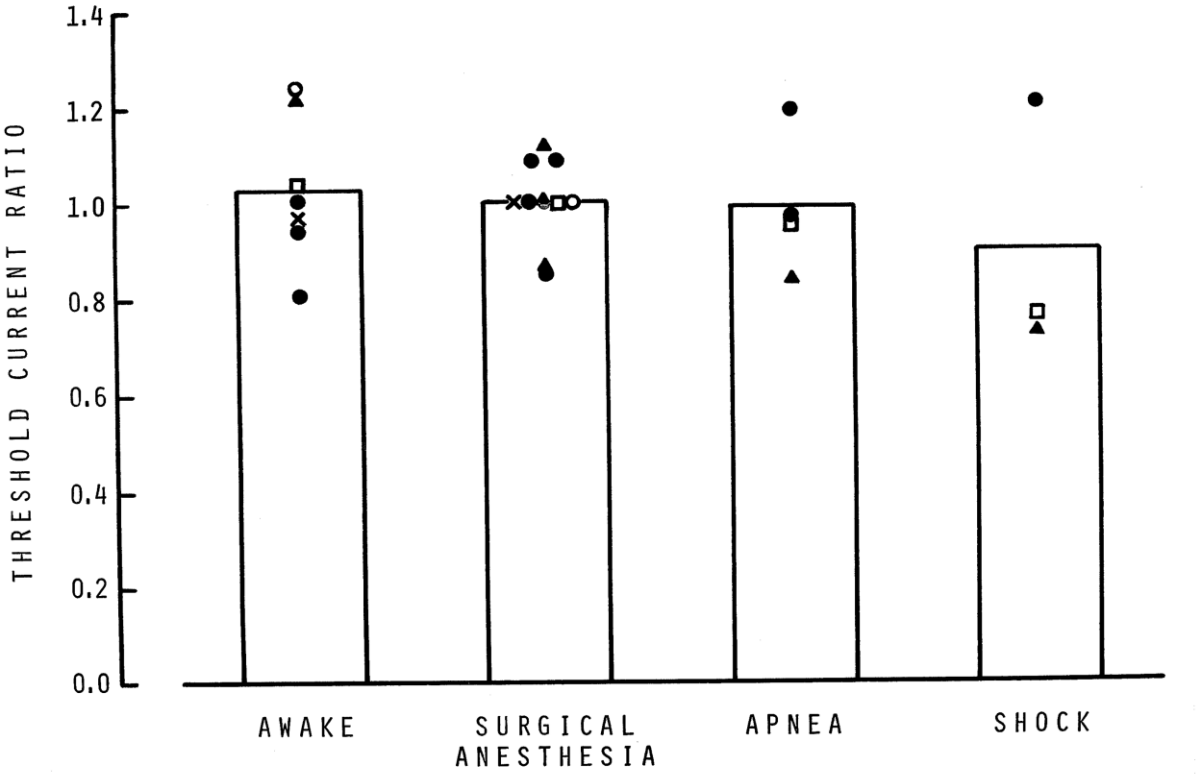

Fig. 2. Relative values of threshold peak current for ventricular defibrillation at four levels of anesthesia. Awake = no anesthesia, surgical anesthesia = spontaneous respiration but no response to surgical stimulation (25 to 30 mg./Kg. pentobarbital), apnea = no spontaneous respiration (42 to 51 mg./Kg. pentobarbital, cumulative dose), shock = aortic blood pressure less than 50 mm. Hg systolic (61 to 77 mg./Kg. pentobarbital, cumulative dose). Mean threshold current under surgical anesthesia = 1.0 for each animal. Dog 1, solid circles; Dog 2, solid triangles; Dog 3, open circles; Dog 4, open squares; Dog 5, crosses.

Study 2. Stability of defibrillation threshold during anesthesia.

Fig. 3 shows the relative threshold current values for five pentobarbital anesthetized dogs as a function of the duration of anesthesia. Relative threshold values were obtained by dividing each threshold current by the mean threshold value for a particular animal. No upward or downward drift of the threshold current is evident. The variation of individual threshold values seldom exceeds ± 10 per cent limits, indicated by dotted lines. Interestingly, the two extreme points in Fig. 2 (Dog 4, arrows) were associated with a bout of acute respiratory failure (arterial blood gases: pH 7.10, pCO_2 54 mm. Hg, pO_2 39 mm. Hg); after the institution of mechanical ventilation in this animal the threshold returned to control levels. With the exception of this incident all dogs exhibited a stable, compensated metabolic acidosis. Arterial blood pH, pCO_2,

and pO_2 averaged 7.36 ± 0.06,* 33 ± 3.7,* and 71 ± 9,* respectively. Mean arterial blood pressure, respiratory minute volume, and urine output were stable during the 8 to 10 hours of pentobarbital anesthesia in all five animals, averaging 127 ± 20* mm. Hg, 457 ± 168* ml./Kg./minute, and 1.2 ± 0.5* ml.i Kg./hr., respectively. (* one standard deviation)

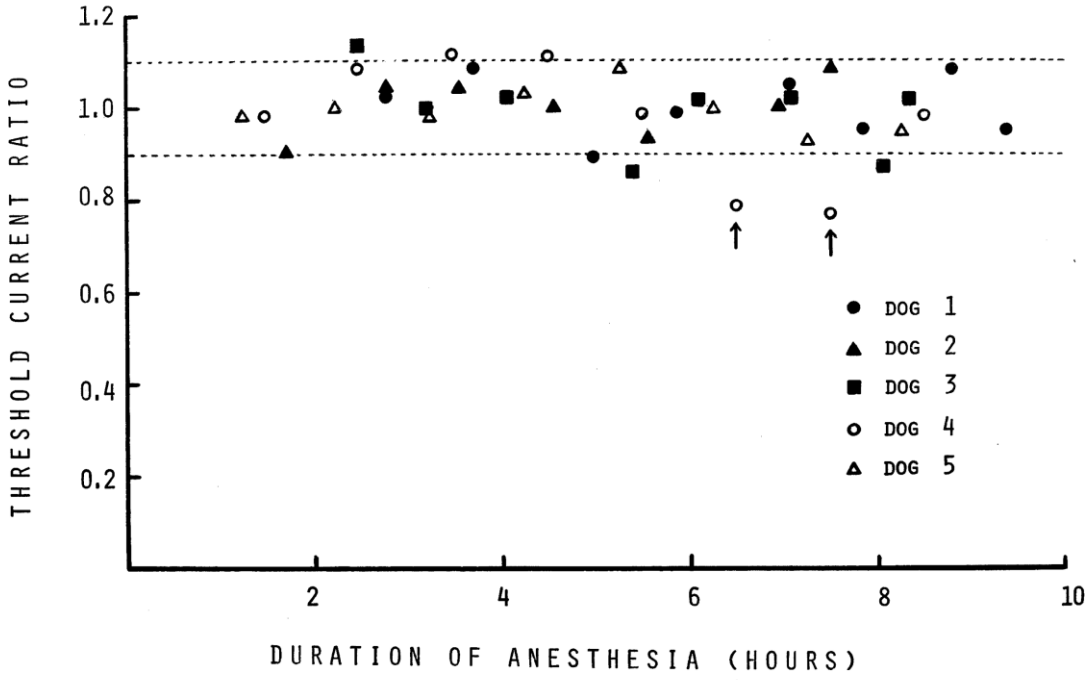

Fig. 3. Stability of ventricular defibrillation threshold during pentobarbital anesthesia in dogs. Mean threshold current = 1.0 for each animal. Arrows indicate threshold values obtained during acute respiratory failure.

DISCUSSION

The data of Studies 1and 2 indicate that the ventricular defibrillation threshold is negligibly affected by either the induction or the maintenance of anesthesia with pentobarbital sodium. This finding is important because so many experimental studies of electrical defibrillation have been carried out in anesthetized animals, whereas in most clinical situations electrical defibrillation is attempted in unanesthetized humans. In view of these results the extrapolation of much hard-won animal data to the human situation may be made with significantly greater assurance. In the absence of surgical or pharmacological intervention, defibrillation threshold is a stable and reproducible parameter in the pentobarbital-anesthetized dog. Demonstration of such a stable baseline paves the way for further studies of drug effects in ventricular defibrillation, in the presence or absence of myocardial ischemia, and for experimental evaluation of alternative techniques of cardiopulmonary resuscitation.

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